## REMARKS

Claims 45-54 and 56-72 are pending in this application. Claims 45-54 and 56-72 are rejected under 35 U.S.C. § 102(e) for anticipation by Poser et al. (U.S. Patent No. 5,968,253; hereinafter "Poser"). Claims 45-54 and 56-72 are rejected under 35 U.S.C. § 103(a) for obviousness over Poser in view of Classen (U.S. Patent No. 5,723,283; hereinafter "Classen") and Relyveld (U.S. Patent No. 4,016,252; hereinafter "Relyveld"). Finally, claims 45-54 and 56-72 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6,214,368 (hereinafter "the '368 patent"), claims 1-7 of U.S. Patent No. 6,117,456 (hereinafter "the '456 patent"), and claims 1-12 of U.S. Patent No. 5,683,461 (hereinafter "the '461 patent"). By this reply, Applicants amend claims 45-46 and 59-61 and address each of the Examiner's rejections below.

### Support for the Amendment

Support for the amendment to claims 45-46 and 59-61 is found in the specification on, e.g., page 7, lines 11-13, page 34, lines 12-13, and page 36, lines 18-19. No new matter is added by the amendment.

### Telephonic Interview

Applicants wish to thank the Examiner for his helpful comments during the telephonic interview of January 18, 2005 with a colleague of the undersigned, Todd Armstrong, in which the 35 U.S.C. § 102(e) rejection of claims 45-54 and 56-72 over Poser and the 35 U.S.C. § 103(a) rejection of claims 45-54 and 56-72 over Poser, Classen, and Relyveld were discussed.

Obviousness-Type Double Patenting Rejections

The Examiner rejects claims 45-54 and 56-72 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of the '368 patent, claims 1-7 of the '456 patent, and claims 1-12 of the '461 patent. In response to the double patenting rejection, Applicants will submit a terminal disclaimer once otherwise allowable subject matter has been determined.

Rejections under 35 U.S.C. § 102

*Poser*

Claims 45-54 and 56-72 are rejected under 35 U.S.C. § 102(e) for anticipation by Poser. The Examiner states:

> Poser discloses paste-like flowable compositions comprising 60-95% tricalcium phosphate, a second calcium phosphate source such as monocalcium phosphate monohydrate in a powder form, in combination with an antibiotic and an aqueous injectable lubricant.
>
> Poser's tricalcium phosphate meets the limitation of the instant calcium phosphate...[and the] antibiotics employed by Poser falls within the scope of the instant claims, because they are capable to [sic] elicit an response against a pathogen in the host. (Office Action, p. 5.)

Applicants respectfully disagree with the Examiner's characterization of Poser, but in the interest of expediting prosecution, claims 45, 46, and 59-61 have been amended to replace the term "active agent" with the narrower term "immunogen." As was discussed during the telephonic interview of January 18, 2005, the present amendment clearly distinguishes Poser's composition, which contains an antimicrobial agent to reduce "the growth rate of microbial organisms in the

region of the product" (i.e., the antimicrobial agent acts directly on the invading organism; col. 6, lines 31-34), from the presently claimed compositions, which contain an immunogen, which is provided to elicit a host immune response that protects the host from an invading organism (i.e., the immunogen acts indirectly on the invading organism by mobilizing the host's own immune defenses). Thus, the Poser composition is distinct from the composition recited in present claims 45-54 and 56-72, and the differences between the two compositions are now even more readily apparent.

The immunological vaccine delivery composition recited in present claims 45-54 and 56-72 is distinct from the antimicrobial agent-containing calcium phosphate composition disclosed by Poser. As is discussed above, independent claims 45, 59, and 60 have been amended to recite an immunological vaccine delivery composition (claim 45), or its use (claims 59 and 60), in which the composition contains a calcium phosphate and an immunogen that elicits a host immune response that protects the host against a pathogen. An "immunogen" is an agent which, when administered to a patient, produces an immune response (e.g., a humoral response involving B cells and/or complement and a cellular response involving, e.g., T cells and natural killer cells; see, e.g., Merriam-Webster Online Dictionary, www.webster.com). The immune response is orchestrated by the body as a means to recognize and defend itself against, e.g., microorganisms, viruses, and substances recognized as foreign and potentially harmful to the body.

The Poser composition, in contrast, contains an antimicrobial agent, which is an agent that destroys or inhibits the growth of microorganisms (see, e.g., "antimicrobial," as defined by Merriam-Webster Online Dictionary). Antimicrobial agents do not assert their microbicidal

activity by activating the host's immune response, as does an immunogen, but rather by acting on the invading microbe directly. Furthermore, an antimicrobial agent that also elicits an immune response when administered to a patient would not be useful and, in fact, would be counterproductive because the immune response would be directed against the antimicrobial agent, not the invading microbe. Because the art distinguishes between immunogens and antimicrobial agents, as is discussed above, present claims 45-54 and 56-58, directed to an immunological vaccine delivery composition containing an immunogen, and claims 59-72, directed to a method of its use, are distinct over the antimicrobial agent-containing composition of Poser. Accordingly, the rejection of claims 45-54 and 56-72 under 35 U.S.C. § 102(e) for anticipation by Poser should be withdrawn.

Rejections under 35 U.S.C. § 103(a)

*Poser, Classen, and Relyveld*

Claims 45-54 and 56-72 are rejected under 35 U.S.C. § 103(a) for obviousness over Poser in view of Classen and Relyveld. The Examiner states:

> Classen describes the use of depot adjuvants such as calcium phosphate salts to prolong the release of [an] immunogenic agent...[while] Relyveld teaches the state of the art for using calcium phosphate to improve the efficacy of vaccine formulations. (Office Action, p. 8.)

The Examiner further states that the skilled artisan would combine Classen and Relyveld with Poser to yield the composition recited in present claims 45-54 and 56-72 because all of the references disclose "various forms of [a] calcium phosphate delivery system," and thus "are viewed to be in the same field of art" (Office Action, p. 8).

During the telephonic interview of January 18, 2004, the Examiner further stated that the

skilled artisan would be motivated to combine Classen and Relyveld with Poser because the skilled artisan would be motivated to employ other known pharmaceutical formulations, such as that disclosed by Poser, to provide an immunological vaccine delivery composition formulated as a flowable, paste-like self-setting composition, such as the composition recited in claims 45-54 and 56-72. Applicants respectfully disagree.

*There is No Motivation to Modify Poser based on Classen and Relyveld*

The M.P.E.P. § 2143.01 states

> Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. (Emphasis added.)

In the present case, the Examiner arrives at the claimed invention by combining references where there is no explicit or implicit suggestion or motivation to do so. The Examiner argues that one of ordinary skill in the art would have modified Poser based on Classen and Relyveld to yield the vaccine composition recited in present claims 45-54 and 56-72 because the skilled artisan would have employed other known pharmaceutical formulations, such as the Poser composition, to deliver vaccines. The rejection is based on erroneous assumptions of fact and, moreover, fails to apply the correct standard for determining obviousness under 35 U.S.C. § 103(a).

The rejection cannot be maintained because it lacks the requisite showing of *motivation* to modify the teachings of Poser. If the "*prior art* does not...provide any reason or motivation to make the modification" alleged in the statement of rejection, there is no obviousness under § 103(a). *In re Laskowski*, 10 USPQ2d 1397, 1398 (Fed. Cir. 1989). The "evidence upon which

the examiner relies must clearly indicate that a worker of routine skill in this art would view the claimed invention as being obvious." *Ex parte Wolters*, 214 USPQ 735, 736 (BPA&I 1982). "It is facts which must support the legal conclusion of obviousness." *Ex parte Crissy*, 201 USPQ 689, 695 (PTO Bd. App. 1976).

> The Patent Office has the initial duty of supplying the factual basis for its rejection. It may not, because *it* may *doubt* that the invention is patentable, resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in the factual basis. *In re Warner*, 154 USPQ 173, 178 (CCPA 1967) (Emphasis in original).

An argument by the PTO is "not prior art." *In re Rijckaert*, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). When the PTO "[a]sserts that there is an explicit or implicit teaching or suggestion in the prior art, it must indicate where such a teaching or suggestion appears *in the reference*." *Id.* at 1957 (emphasis added).

The Office Action and the Examiner's statements during the telephonic interview of January 18, 2005 fail to explain where the alleged motivation can be found in the prior art, i.e., on what basis "the skilled artisan would have been motivated" to modify the Poser composition to provide a vaccine formulation based on Classen and Relyveld. Clearly, the requisite *motivation* necessary to show obviousness under 35 U.S.C. § 103(a) has not been established, *Laskowski, supra*, and, since the *initial* burden to do so rests with the PTO, *Oetiker, supra*, withdrawal of the rejection under 35 U.S.C. § 103(a) is in order.

Moreover, the Examiner's basis for the rejection appears not to take into account motivation. Merely having the *means* in the prior art to achieve a desired *idea*, i.e., a flowable, paste-like calcium phosphate material that could be mixed with an immunogen, is an insufficient basis for an obiousness rejection *unless* the prior art also teaches or suggests the *idea*. Invention

involves both the *idea* of the invention as well as the *means* to achieve the desired idea, and both the idea and the means must be found in the prior art to negate patentability. *Oka v. Yossefyeh*, 7 USPQ2d 1169 (Fed. Cir. 1986). *In re Hoffman*, 37 USPQ 222 (CCPA 1938).

The Examiner's basis for the rejection of claims 45-54 and 56-72 for obviousness is merely that the *means* to achieve the idea would have been known to one skilled in the art. The "argument that undirected skill of one in the pertinent art is an adequate substitute for statutory prior art" is "rejected." *In re Kratz*, 201 USPQ 71, 76 (CCPA 1979). When

> comments regarding obviousness amount to an assertion that "one of ordinary skill in the relevant art would have been able to arrive at [the claimed] invention because he had the necessary skills to carry out the requisite process steps[,] [t]his is an inappropriate standard for obviousness."

*Ex parte Levengood*, 28 USPQ2d 1300, 1301 (BPA&I 1993).

> The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification.

*In re Fritch*, 23 USPQ2d 1780, 1783-84 (Fed. Cir. 1992).

The composition of present claims 45-54 and 56-58, containing a calcium phosphate formulated as a hardenable, injectable paste having a solids content of greater than or equal to 40 wt% and containing an immunogen which elicits a protective host immune response against a pathogen, was not obvious.

As is discussed above, Poser discloses a flowable, paste-like setting calcium phosphate composition containing an antimicrobial agent, which is administered to reduce the growth of bacteria in a host (see, e.g., the abstract). Poser fails to teach or suggest that the antimicrobial agent-containing composition is provided to elicit a host immune response that then protects the host against a pathogen, or that the composition can be used as an immunological vaccine

delivery composition to deliver an immunogen, as is recited in present claim 45, and claims dependent therefrom. Poser lacks any teaching or suggestion to employ the composition as an immunological vaccine delivery formulation, and thus, fails to provide the motivation or guidance, explicitly or implicitly, to direct the skilled artisan to appropriate Poser's calcium phosphate composition to deliver vaccines.

Classen and Relyveld, which disclose vaccine formulations for the administration of immunogens, also fail to provide the motivation or guidance to direct the skilled artisan to look to Poser to formulate the immunological vaccine delivery composition recited in claims 45-54 and 56-72. Classen discloses a method of determining whether an immunization schedule affects the incidence or severity of a chronic immune-mediated disorder by immunizing a mammal with one or more doses of one or more immunogens, according to an immunization schedule (see, e.g., the abstract and claim 1). Classen discloses a traditional vaccine formulation that contains, *inter alia*, an immunogen (see, e.g., col. 15, line 30, through col. 20, line 34) and an adjuvant (e.g., calcium phosphate salts; col. 20, lines 35-50), which are diluted in phosphate buffered saline (PBS; see, e.g., col. 35, lines 23-38). Classen fails to teach or suggest the administration of an immunogen using any calcium phosphate composition, let alone such a composition having a solids content of greater than or equal to 40 wt% and that is hardenable. Like Poser, Classen contains nothing to suggest combining Poser and Classen. Classen fails to provide the requisite motivation to modify the calcium phosphate salts in the Classen composition to yield a vaccine formulation provided as a flowable, paste-like self-setting composition, such as that recited in claims 45-54 and 56-72, based on the disclosure of Poser.

Relyveld discloses an aqueous gel of calcium phosphate for preparing adsorbed vaccines (see, e.g., the abstract). The calcium phosphate-based vaccine formulation of Relyveld contains a solids content two orders of magnitude less than the adjuvant composition of present claim 45, and Relyveld fails to teach or suggest the skilled artisan to prepare a vaccine formulation with a higher solids content. In fact, Relyveld discloses that

> it is highly desirable that the particles of the suspension be as fine as possible. This requirement is well met by the gel of the present invention, which exhibits a marked colloidal character. The fineness of particles in the gel of the invention is demonstrated by the fact that the velocity of settling of the gel is much slower than that of conventional calcium phosphate gel. (Col. 2, lines 2-9; emphasis added.)

Therefore, Relyveld clearly discloses that the calcium phosphate gel should be administered as a fine, particulate formulation; a disclosure that directly teaches away from the composition recited in present claims 45-54 and 56-72, which is a hardenable, injectable paste having a solids content of greater than or equal to 40 wt% (M.P.E.P. § 2144.05(III)).

Although it could be argued that the skilled artisan would have reason to combine Classen with Relyveld, because both of these references are directed to vaccine formulations containing calcium phosphate as a fine particulate, the skilled artisan would have no reason to further combine these references with Poser, which is directed to an antimicrobial agent-containing calcium phosphate cement composition that is not used for vaccination purposes, and provides no motivation to use the composition for this purpose. Therefore, the skilled artisan would have no motivation to combine references related to vaccine formulations (Classen and Relyveld), with a reference related to the delivery of an antimicrobial agent (Constantz) due to their disparate teachings, much less to modify these disclosures to produce the immunological vaccine delivery composition of present claims 45-54 and 56-58.

In addition, nothing in the prior art would have motivated one of ordinary skill in the art to dramatically change the established working concentrations of a vaccine formulation having a low solids content of 0.5-3.3 wt %, as is disclosed by Relyveld, to greater than or equal to 40 wt %, as is recited in present claims 45-54 and 56-58, based solely on the disclosure of Poser, especially when Classen and Relyveld clearly show efficacy of the low solids content compositions for use as adjuvants and Poser says absolutely nothing which would suggest the use of calcium phosphate compositions to elicit an immune response. The Examiner argues that one skilled in the art would have modified Poser based on Classen and Relyveld to employ Poser's pharmaceutical formulation to deliver an immunogen based solely on the fact that the skilled artisan would look to other calcium phosphate delivery systems to deliver vaccines (Telephonic interview of January 18, 2005). As is discussed above, this position lacks merit because the Examiner fails to show that the *prior art* provides any motivation to modify Poser based on Classen and Relyveld, which is a required element of 35 U.S.C. § 103(a) (M.P.E.P. § 2143.01, *supra*), and, furthermore, Relyveld clearly teaches away from this modification (see Col. 2, lines 2-9). Accordingly, the Examiner has relied solely on the knowledge of the skilled artisan and his own erroneous assumptions of fact to establish the obviousness rejection, both of which are an improper basis for rejecting claims 45-54 and 56-72 for obviousness (*Ex parte Levengood*, *supra*; *In re Zurko*, *supra*). Therefore, to meet his burden, the Examiner must provide some concrete evidence or objective reason why the skilled artisan would combine and modify the disclosure of Poser, Classen, and Relyveld to arrive at the invention of present claims 45-54 and 56-72. Simply stating that the skilled artisan "would have modified" the vaccine formulation of Poser based on Classen and Relyveld does not rise to the level of "concrete evidence" or an "objective

reason" why the references should be combined and modified. Absent such evidence, or objective reason, Applicants respectfully request that the rejection of claims 45-54 and 56-72 under 35 U.S.C. § 103(a) over the combination of Poser, Classen, and Relyveld be withdrawn.

Applicants also wish to briefly address the Examiner's comments during the telephonic interview of January 18, 2005, in which the Examiner argued that the skilled artisan would view Poser as being in the field of immunology and would be motivated to use the antimicrobial agent-containing composition of Poser as a vaccine delivery system because antimicrobial agents result in the production of cytokines, and thus, would promote a protective immune response. Applicants respectfully disagree.

Applicants wish to direct the Examiner to Schultz et al. (Antimicrobial Agents and Chemotherapy, 42:1605-1609, 1998; a copy of which is provided) and Morikawa et al. (Antimicrobial Agents and Chemotherapy, 40:1366-1370, 1996; a copy of which is provided), which were published prior to the filing date of Applicants' application and which disclose that antibiotics have an immunosuppressive effect on the production of cytokines, namely, tumor necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6); inflammatory cytokines that are involved in the host response against pathogens. Schultz et al. report that the administration of erythromycin to human patients inhibited the production of inflammatory cytokines in response to an immunological challenge with *Streptococcus pneumoniae*, and thus, "may negatively influence specific host defense mechanisms during pneumococcal pneumonia. Together with other reported anti-inflammatory effects of macrolides, these data indicate that, during the treatment of pneumonia, the immunomodulatory actions of this group of antibiotics may well be a disadvantage with respect to clearance of the infection" (see page 1608, col. 2).

Morikawa et al. disclose that fosfomycin (FOM) and clarithromycin (CAM) modulated the release of cytokines by LPS-stimulated human monocytes (see, e.g., page 1368, cols. 1 and 2), reporting that FOM and CAM suppressed the synthesis of IL-1α, IL-1β, TNF-α, and GMSCF by monocytes (page 1368, col. 2) and weakly inhibited the production of IL-1ra (page 1368, col. 2), while FOM enhanced and CAM weakly inhibited the production of IL-6. Morikawa et al. conclude by stating that "some antibacterial drugs may modify the acute-phase inflammatory response by disturbing the cytokine cascade" (page 1369, col. 2). Thus, the benefit of administering an antimicrobial agent as or with a vaccine formulation has been questioned in the art due to the suppression of cytokine production, by the antimicrobial agent, which results in a diminished host immune response. Because Poser lacks any explicit or implicit teaching or suggestion to use his antimicrobial-agent containing calcium phosphate cement composition as a vaccine delivery system, and because the prior art cautions against administering antimicrobials in connection with vaccines, Applicants again submit that the combination of Poser, Classen, and Relyveld is improper and the rejection of claims 45-54 and 56-72 under 35 U.S.C. § 103(a) should be withdrawn.

## CONCLUSION

In view of the above remarks, Applicants respectfully submit that the claims are in condition for allowance, and such action is respectfully requested.

Enclosed is a petition to extend the period for replying for three months, to and including March 22, 2005, and a check for the fee required under 37 C.F.R. § 1.17(a).

If there are any other charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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